Having said that, I would say that this is not a good device to close unoperated post-infarction VSDs and I wouldn't do it.

DR. AZIZ: What about in the primary situation?.

DR. LOCK: Post-infarction VSDs that have not already undergone surgery to fix their coronary artery disease, our results have not been good and I don't think this is a good device for that clinical situation. The holes are all 10 mm, 12 mm.

When you put a device in the septum' continues to resorb and the infarct gets bigger and the hole gets bigger. While you may stabilize them for 12 to 36 hours, the holes invariably have come back in the unoperated first five-day post-infarction VSDs.

The successes that we've had, and I don't know what the number is but it's maybe half, I think have all been post-operative, or all but one have been surgery to fix the coronaries, to fix the VSDs, the defect has recurred and that's when we have gone back and made those patients better.

DR. AZIZ: You couldn't see this being used as a bridge to sort of stabilizing the patient for five or six days and then going in?

DR. LOCK: I think there is a new device that's in development which is much larger and has partial self-centering characteristics and might, in fact, be a very successful device for stabilizing. We hope to start using that device for post-infarction VSDs but not device. I'm not going to use this device for post-infarction VSDs anymore.

DR. AZIZ: Thanks.

DR. HOPKINS: I'll echo some of the other panelists. I don't think you see a lot of surgeons fighting for these patients. I think the major outcome of significance is really the survival some six to 12 months after you've had to do something of which this is a good choice.

I am interested about the thoughts about the post-infarction VSD. I, too, was going to ask about that. In your indications for use, there's no specific either indication or contraindication for its use in that subset of patients.

If you feel strongly that it should not be used, I just wonder. I just throw it out and suggest that perhaps that should be put in as a contraindication to its use or, at least, a lack of indication.

A question of there were two devices. As I read through the various sections it appeared that in the pivotal series there were two devices which were explanted at surgery that were not one of the mortalities. Does anybody know the story on those two patients or why?

DR. JENKINS: Two were at heart transplantation for ventricular failure. One was a failed septation that was taken out at the time of a Fontan operation. It was basically a failed procedure. The fourth explant was done in the cath lab. It was that same patient who had the four embolizations. One of the devices got taken out late and that patient ultimately went to the operating room.

DR. HOPKINS: That was taken out transcatheter.

DR. JENKINS: Yes, it, was.

DR. HOPKINS: There were two.

DR. JENKINS: There were three. Two at transplant and one at Fontan.

DR. HOPKINS: Two surgical.

DR. JENKINS: And one at Fontan.

DR. HOPKINS: Okay. Thanks. In the summary of safety and effectiveness, as well as in the indications for use -- and there have been a number of references to this. Some references to poor anatomy as being a contraindication or bad anatomy or unfavorable anatomy for its use -- and sort of left it at that in terms of a qualitative sort of statement.

Can you provide more precise guidance for what constitutes bad anatomy for its use or should that be more specifically part of the training component? Is there some quantitative approach within 2 mm of the mitral valve, etc.?

MS. KULIS: Certainly we can add additional detail as far as what anatomy is unfavorable.

Dr. Jenkins?

DR. JENKINS: It will primarily be with

relation to the valves. I don't know if one of the interventionalists could comment on anatomy where it's just not technically possible to pass a sheath or a wire through such an extraordinary pathway.

DR. HOPKINS: I just want you to know it's being used now in just a couple of superb centers. As it spreads out, I'm just wondering if there doesn't need to be a little bit better guidance for those.

MS. KULIS: I'd just like to make one point as far as you said used in a couple of centers. We have a total of 30 centers right now in the United States that do have institutional approval to perform VSD closures using this device.

DR. HOYER: Mark Hoyer again. As far as location of defects and difficult ones to get to, obviously I told you we have done three so I don't have an extensive experience that I'm going to be able to convince a lot of people but I can tell you that down at the apex of the heart it can be very cumbersome.

There's a lot of trabeculations in the right ventricular side of the septum. In fact, the device

won't necessarily even open completely so that it's flat on both sides but it will be darn close. But you still have accomplished the task of opening the left ventricular side and then releasing the device as you open up the right ventricular side before letting go of it and is in a stable position. Perfectly stable. That, again, is a muscular defect much closer to the apex but well away from semilunar valve or AV valve.

DR. BOUCEK: Yes. I think you're correct that there are some locations where it is more difficult in the anterior portion of the septum sometimes it's difficult to get the sheath to go up into that portion. These are difficult procedures to begin with. I think they represent the sort of new unfortunate era, if you happen to be an interventional cardiologist, of where pediatric cardiology interventions are going.

I think with experience with other types of complex interventional procedures in pediatrics, it's just a matter of a problem to be solved rather than an insurmountable problem. It tends to be lengthy.

Sometimes you have to try the sheath from a different approach rather than from the neck. Maybe from below. It ends up being problems that need to be surmounted rather than ones that shouldn't be attempted. They tend to be long cases. They are like some of the more complex oblation procedures or some of the more complex stent procedures that we do in terms of the duration of time that we're in the cath lab. I finally understand how much I respect the surgeons for spending eight hours in the operating room.

DR. HOPKINS: Well, don't misunderstand me. I'm not going to 'sign up to get trained on this device. I think that, in fact, I am on your side on this. I want this to succeed as it rolls out. I'm just concerned about the training. I think we'll probably talk about training a little bit later, but that there be a little bit more precision in the guidance of this.

I think, also, knowing these patients and looking at the study information and also reading between the lines, these are patients that are being managed in centers that have full cardiac surgical

backup.

In the indications for use and guidance documents, it basically says surgical support should be readily available. I think that may be more bland than it needs to be. I think this needs to be done in centers where it is truly complete support.

Also you talk about the' transient hemodynamic compromises. It sounds to me like the reason the mortality rate in this extraordinarily difficult group that you presented being so low is that they are managed by cardiac anesthesia, cardiology, interventionists simultaneously.

I wonder if there shouldn't be a little more stronger guidance about that either in the training document or in the indications for use because this is not your standard coronary stent that's going in. You're using a whole team approach here.

Like others, I congratulate you.

DR. TRACY: Dr. Zahka.

DR. ZAHKA: This is certainly a very diverse group of patients and a very challenging group of patients. You all deserve congratulations as well.

The assessment of them is not always easy as evidenced by the child with a single ventricle that was attempted to be septated, and the 12 patients who were felt to have larger VSDs and turned out to be small. Did those patients have a band on that made it impossible to really judge the VSD size, the 12 patients that got enrolled but did not get implants.

DR. JENKINS: Had no intent of planting a device. Part of that is factual just in the way that we set up the study because we had to have the prior pier review. There was a lot of paperwork that had to be done just to have it possible to put a device in at the time of the procedure.

In order to have the procedure go forward in a timely fashion, we tried to anticipate cases where it might be necessary even before the hemodynamics had been done. Obviously everyone is always hoping these defects go away on their own and they sometimes do.

DR. ZAHKA: Does that then reflect our inability to really assess these people, these children accurately and how does that speak to the follow-up data?

DR. JENKINS: I think assessment has to be made in the cath lab once the final pictures are there. For the band patients it's very difficult for the echocardiographers to always judge appropriately. Even for the nonbanded patients I think the angiograms and the hemodynamics help a lot.

I think in this case, though, it's partly an artifactual reflection that if there was even a small probability like 15 or 20 percent likelihood we might want to close a defect. We did peer review of the patients so then they are counted as enrolled in the study.

DR. ZAHKA: It's also been my sense, in fact, that infant cardiac surgery has progressed dramatically over the last 12 years. Although there's not a lot in the literature about closure of multiple muscular VSDs and that there are still problems with that, that this process has, in fact, progressed and that there are probably more children who could be done surgically as well.

I look at the illustration in the operator's manual of this ventricular septal defect which looks

like it would be good to close by intervention or by surgery. Perhaps what is the risk benefit of each at what age.

I think about the process you have for reviewing who should be enrolled in this approach and notice that you have a surgeon and a cardiologist review every case beforehand. Is that surgeon and cardiologist also part of Boston Children's Hospital or are they kind of separated from this whole process?

DR. JENKINS: They are within our institution. The reason we did that was simply for expediency except for the adults enrolled in the trial where the peer reviews are done by adult cardiologists at partnership centers. The peer reviews at all the centers in the trial, that was similarly the case.

I think that some of it is taken as a success if the surgeons get better partly because of some of the alternatives that patients have available. I think in response to Dr. Skorton's earlier question, I did do a pretty extensive literary review looking for almost anything that was more recent than what Dr. Mayer presented.

What I found was a series of 11 cases in Dr. Bovey's paper that was buried between categories where they weren't really broken down by ventriculotomy. That group of 11, according to the authors of that manuscript, it does suggest that maybe some left ventriculotomies are doing a little better than they were, you know, 10 or 15 years ago.

There was only one other single case report from the European literature where a large ventriculotomy was presented as a good outcome short term. There was a series of letters to the editor afterwards, you know, kind of worrying about late results. That was all I found in the literature.

If it's true that the surgeons are doing better, it's not out there where we can review it and see the results. I'm sure there's going to be a series of defects that are always difficult to close surgically, a series that are easy to close surgically and a series in between where, you know, the cardiac surgeons will evaluate the best outcome as time passes.

DR. TRACY: Dr. Williams.

DR. WILLIAMS: Well, my questions will be related to what is the best way to transfer the experience at Boston Children's Hospital to other institutions as they become involved. And if there should be any limits on the kinds of patients that are attempted by hospitals earlier in their learning curve or who have a lower total volume experience with surgery, echo, and the other factors that are important to this process.

The first one was the illustration showed passage of the catheters through the simplest kind of lobe and muscular defect. Then we heard that the adverse events were more related to technical issues.

I have a suspicion that maybe technical issues were greater in the far interior or far posterior or apical positions. Were you able to look at those separately to see if those kinds of defects had a higher incidence of adverse events than the more favorable position?

DR. JENKINS: We looked at the differences in outcomes by the post-operative residual defects versus the congenital defects and we didn't really

find any differences in our safety or efficacy outcomes for those two groups but we never looked by the specific location in the septum where the defects were-.

DR. WILLIAMS: I wonder if Jim Lock, who has such large experience with this, has an impression?

DR. LOCK: I think Dr. Williams is correct. One can predict where the trouble will occur from choosing catheter passage. I do believe that most of the catheter induced -- most of those five patients with catheter induced heart block were posterior muscular VSDs near the tricuspid valve.

I do think that the patients with the catheter induced mitral regurgitation were also posterior muscular VSDs. That is the particular -- if you were going to -- 1 think actually the anterior septum turns out to be the easiest and the safest place to fool around.

I think if you were going to apical muscular VSDs, mid-muscular VSDs, intramural VSDs near the aortic valve are actually pretty safe. I think the one place where people should be more cautious really

in their experience is in the posterior muscular septum near the attachment to the tricuspid valve.

DR. WILLIAMS: Thank you. You might want to keep your seat because I've got another question coming up.

It seems to me that considering the difficulty sometimes intellingthe difference between multiple VSDs and a patient who really truly has no septum but has bundles that are running at different angles to each other, essentially have no wall but a collection of bundles, in high referral centers by echo you often see this as a misdiagnosis from other centers. I think even in the best of hands it's possible to miss it. I think probably it was.

I would say that probably echo is superior to angiography in recognizing this lesion if it's done very, very carefully. I think MRI in some circumstances can also add some information.

My question is really what should be the experience requirements for the echo cardiography who is evaluating these patients prior to attempt or prior to talking to the family about the potential for doing

a device closure.

And if there might be some way where the mother institution could produce a teaching tape or a series of teaching evaluations to show echocardiographers how to recognize this lesion -- it ought to be done anyway -- in order to avoid this particular pitfall.

Or how to recognize what you would view as the higher risk defects and how to recognize that margin along the posterior -- that posterior margin of the defect, where you think the pitfalls are so they are not going to be able to recognize this with their lower volume and lower experience. Is there a way to shorten the experience, the learning curve?

DR. LOCK: Yes. You're exactly right. I mean, if you look carefully at the data, we made that mistake three times. We thought there were three patients that were septable that probably really weren't and they had exactly the anatomy that you describe, and that is that you could sort of talk yourself into thinking there was a septum but then when the surgeon goes in, there just is not a septum.

We will and have analyzed those three patients and will continue 'to do so.

I think you are right. Sophisticated echocardiography and probably 3-D reconstruction is a better way to assess this than angiographically which was inferior to those two techniques in deciding who is septable and who isn't. I would agree that is part of our responsibility.

DR. WILLIAMS: And I think that will be part of the general recommendation on my part that when you talk about what are the institutional requirements to carry this out, that it specifically states training and experience requirements for the echocardiographer and the cardiac anesthesiologist since the total outcome is so dependent upon those individuals as well as the main operator.

Could I just ask in the far anterior and far posterior defects, I recognize that this device is flexible and soft. It's not likely to impinge on structures so much. Has there been any indication of interference with the anterior or posterior descending coronary artery and would you have recognized it given

the kind of surveillance? What would you expect to have seen if you had encountered that?

DR. LOCK: We haven't done selective coronaries in any of- the patients. The only thing that I tried to do, and I'm not sure this is an adequate test, obviously we tried to look at ventricular performance in all of the patients and haven't recognized to my knowledge localized ventricular dysfunction.

There's no question that the device can sit right next to the septum and, therefore, you know, one of the anterior or posterior descending arteries. We just haven't seen it.

DR. WILLIAMS: Okay. So you haven't seen segmental wall motion?

DR. LOCK: We look pretty carefully for it because obviously it was one of the clinical concerns about ventriculotomy patients.

DR. JENKINS: We haven't seen signs of ischemia on the electrocardiograms or things like that on the surveillance.

DR. WILLIAMS: Okay. Great. Do you believe

the best use of this device in those patients who have complex conal truncal abnormalities or pulmonary artery bands is ultimately to do the catheter closure after you've attempted to do the surgical closure or to do the catheter closures of the more difficult defects in preparation for attempting as a stage before deciding whether to attempt a complete repair?

DR. LOCK: We do it both ways. I think that if the patient has a band in place, then we tend to close everything we can close safely in the cath lab. If the patient doesn't have a band in place rather than commit the patient to two cardiac operations, the surgeons decide if they think they can close most, if not all, of the defects.

If they think they can close most, if not all, the defects using John's requirements without a left ventriculotomy or without an extensive right ventriculotomy, then they get the first crack at those patients. It's really very patient dependent.

DR. WILLIAMS: Given the variation of surgical experience with these lesions, do you recommend to other institutions that they do it one

way before doing it another?

DR. LOCK: I think the safest technique now is bands for people with multiple muscular VSDs.

DR. WILLIAMS: But rather if you anticipate you might need to do both, which one to do first for those institutions that may have variable surgical experience?

DR. LOCK: I think the risk of catheter closure in banded patients is actually pretty small.

DR. WILLIAMS: And since the indications of the catheter closure are so closely related to the ability of the surgeon to close defects, particularly if you're going to do the surgery anyway, do you have any recommendations on the volume experience of the surgical team or the institution in terms, of surgical experience knowing that by your studies and others have been directly related to surgical outcome? I'm sorry to be asking all these questions.

DR. JENKINS: The wrong hat, Roberta. I'm not sure what specific volume standard, for that would be or whether a volume standard is the correct measure. I do know that through the Agency for Health

Care and Research that there is going to be a proposed volume standard of around 100 surgical cases a year being dictated to pediatric cardiology based on relatively little information. Whether that would apply to a specific patient with complex ventricle septum I think would be hard to say.

I think at this point one would need to emphasize that if the surgeon is wrong and they can't close these multiple defects safely, that the patient is likely to be very sick and the patients where we did it in the opposite direction and the VSD was left are often taken to the cath lab for a VSD closure on a fairly urgent basis.

I think in those cases where people were less certain about what they could do, it would be impprtant to have really all of the alternatives available in order to get safely to the other side. It's a bit of a judgment call whether you would do the device first or the surgery first and hope for the best with the device later if the surgeon wasn't able to accomplish everything they had hoped to do.

DR. WILLIAMS: In the larger scheme of

things whether one should use device closures at all in centers that are not large volume experienced centers. I think this comes to the question of whether one should electively regionalize the sickest of the sick patients with known complex disease.

One easy question to end. There seems to be more fractures for the PFOs, 37 percent, than for the ASDs, 15 percent. Is that because the septum flops around more and it bends it more or is that incorrect?

DR. GAWREAU: We've actually noticed that larger devices are more likely to fracture. Larger devices are needed to close the PFOs and that's why you see the larger fracture rate and the higher fracture.

DR. WILLIAMS: Thanks.

DR. TRACY: Dr. White.

DR. WHITE: What are you planning to do about nickel- allergy?

DR. JENKINS: We actually have a lot to say about nickel and also nickel allusion. I think I'm going to refer that question to Carol Ryan, the engineer on the project because there are issues

beyond nickel allergy.

MS. RYAN: We've gotten that question many times and actually looked at that very early on in the design process. Significant studies were done to look at the medal ion to solution rates to be assured that they were very low. Significant literature searches have been done and discussions' with multiple consultants regarding nickel allergy.

The one paper I tend to refer cardiologists to now when they ask that question because they have a patient with nickel allergies, a paper written by Katherine Merritt who actually works for the FDA. She did a nice summary on immune responses to metallic devices and their leechables.

Her conclusions were that -- she basically looked at all the literature that's out there as well as her own studies -- that there is no obvious relationship between a dermal response and a systemic one.

Her recommendation is that surgeons or clinicians should not deviate from their normal surgical practices based upon if a patient has a

nickel allergy or an aliergy to any sort of metal ion. Devices should be designed so that the metal ion to solution rates are kept to the lowest possible amount and that was pretty much our conclusion.

I can think of at least 10 accounts to date where we've been approached because a patient was allergic to nickel and they've received a device and we've had no adverse reports from that usage. The ion to solution rates for this device are actually extremely low. All the possible metal ions that could leech out of it were evaluated. In most cases they' were undectable levels.

DR. WHITE: The second thing I have to say is a minor one. In Section 49.2 you describes the device as being 11 French and I think you've said today that it's 10.

MS. RYAN: It's 10.

DR. WHITE: You need to fix that.

Can you tell me, just educate me, in your tables about how well the patients did on one of the slides here, it says, "Clinical status CL by patient VSD pivotal cohort." Why did you assess the benefit

by median scale value? Why did you not use mean? Is there something about an ordinal scale evaluation that I don't understand?

DR. GAUVREAU: When you're working with an ordinal scale it's more appropriate to use medians rather than means. One reason is that the data are usually not normally distributed. The second reason is something I had mentioned earlier where the difference between a two and a three is not the same as the difference between a three and a four. It doesn't make sense to use means.

DR. WHITE: Fair enough. In terms of the doctor training in Section 5 you have several classes of physicians outlined. The third class is a fellowship trained doctor who you state may or may not have had a lot of experience. You were going to have your representative decide whether he needed to have Category II or Category IV training.

DR. JENKINS: I think that would depend on where the fellowship training was. For example, there are some people who spend an entire year in inte-rventional training fellowship.

DR. WHITE: What I'm suggesting is that you delete the class and that you make your decision based upon whether the physician is qualified with implant or not. He's either a two or a four.

DR. JENKINS: Okay. I understand.

DR. WHITE: Take away No. 3. There's no point in that. You save the embarrassment. You save your company walking up to a young doctor who thinks he knows what he's doing and you have to tell him he doesn't. It's never very pleasant.

The other thing is that under No. 4 you talk about proctoring doctors but 'you don't specify the number of cases that will be done. Have you given that any thought? How many cases will a proctor take an experienced physician and when is it enough?

MS. KULIS: Certainly, I'll ask Dr. Jenkins or one of the other clinicians to elaborate but as a company we thought that a minimum of five proctor cases would be what we would consider acceptable before we would certify the site to receive devices.

DR. WHITE: Given that this busy hospital did 57 in four years, how long is it going to take

somebody to get proctored?

DR. JENKINS: I think we would be very open to suggestions about how the training should be done for this project.

DR. WHITE: Okay. I think that it's a very complicated procedure. I don't do this procedure but it looks as if more than half your patients had multiple devices placed and that more than two operators participated in 67 percent of your cases. It sounds like a little bit different than closing an ASD. I'm a little concerned about the infrequency of the procedure and then how are you going to get people trained to do this.

I don't want to be rude but I would challenge your primary endpoint. Everybody here seems real happy that you've done this but I'm not happy. I'm used to endpoints that say that we had a procedure success and no major complication.

If you subject your data to that analysis, how many of your patients were successfully closed and walked or crawled out of the cath lab without a major complication? It seems to me like so many patients

had big complications that not very many people got out of this unscathed.

DR. JENKINS: I guess the question would be whether you mean a manageable complication or something that would meet a definition of a serious hemodynamic impairment. .I think if you use --

DR. WHITE: Most of the time we don't get to make excuses. I mean, you set an endpoint and you say procedure success or technical success is deployment of the device. Procedure success is successful technical deployment with no major complication. You get to pick what your major complications are. Under those criteria what would be your --

DR. JENKINS: In those criteria I would have personally chosen probably survival as my outcome so we might have disagreed on what was the major complication.

DR. WHITE: I guess what I'm saying is that your ordinal scale has its own merits or demerits but you're not balancing a successful procedure with a pretty bad complication may not be such a desirable outcome.

DR. JENKINS: We didn't create a composite endpoint for this study. We gave the safety data and the efficacy data in parallel without an overall measure that combined the two.

DR. WHITE: I don't want you to think I'm being unreasonable. I understand that you can take a band off the kid and, you know, the baby is better than he was without the band off.

It's just that everything else we think about has to be graded according to the risk benefit and so you don't get to claim a success if you have a major complication even if technically the procedure was effective.

What is a STARFlex? You had three patients crossover to STARFlex. Is that a competitive device or is that just another iteration?

DR. JENKINS: It's the third generation of this one that has been introduced.

DR. WHITE: Of this device?

DR. JENKINS: Yes. There's not as of yet sufficient STARFlex data to put before our panel.

DR. WHITE: Why did you cross patients to

the newer device?

DR. JENKINS,: They weren't crossed over. The device was introduced within the time frame where the CardioSEAL was -- the CardioSEAL is still available in this study and it's the selection-.of the implanting cardiologist whether ,a CardioSEAL or a STARFlex is chosen.

They weren't crossed over to a STARFlex but we were just being strict that when we gave you information on all VSDs enrolled through 2/1 2000 there were three that were not enrolled with CardioSEALs that were not included in this data summary. Maybe I'm not being clear. They didn't crossover into a STARFlex.

DR. WHITE: How did they get a STARFlex and get reported in this database?

DR. JENKINS: They are not reported in the database. That's the point. We gave you data through 2/1 2000, all of the VSDs that were enrolled in the trial.

DR. WHITE: In this trial?

DR. JENKINS: In this trial. Everyone that

was enrolled through 2/1 2000 but we're only reporting on -- excuse me?

DR. WHITE: Where are the three STARFlex patients?

DR. JENKINS: The STARFlex was introduced into the study in the early part of 2000. There happened to be three patients who met that definitional criteria who had a VSD who were enrolled in the study who were included in the overall dataset.

But because this particular part of the data was intended to show the performance of CardioSEAL, the STARFlex patients were not included in the 57. However, just to be maybe ultra conservative in our reporting, we told you that there were three that fell within the time frame of our enrollment.

DR. WHITE: So have you now gone past the CardioSEAL device and' are using STARFlex for this disease?

DR. JENKINS: At the Children's since we -have the STARFlex device for the high risk trial on an ongoing basis, VSDs are being done with both of the devices but quite a few of the recent ones are being

done with the STARFlex.

DR. WHITE: Why did you choose not to include the catheterization complications when you reported the adverse events? You told me that out of the 222 total adverse events, there were 32 that were device related and 35 that were implantation related and 85 that were related to the cath. But when you went to look at the summary of the adverse events, you didn't include cath complications in that.

DR. JENKINS: They are all in the Panel Pack in exhaustive detail.

DR. WHITE: I mean in the --

DR. JENKINS: In the primary income.

DR. WHITE: You said you were interested in the --

DR. JENKINS: The reason is that we chose -- the reason is that most patients would be having a catheterization anyway. That's the spirit of choosing the outcome as the specific part of the study whereby the device was placed or the implant procedure was done.

What we did instead is that our safety

committee spent an inordinate amount of time figuring out if a specific event was due to the implant part of the procedures, or do just having a catheterization. They made that distinction.

With them having done that, we counted as the primary safety outcome just the device or the specific part of the procedure where the large sheaths and the wires and all that were in the heart rather than simple things that were just the result of a patient having a cath.

DR. WHITE: Well, the problem with that is that because you're not comparing this to anything else and the catheterization is integral to the device implantation and delivery, it's a little bit disingenuous. It makes the procedure seem safer than it might actually be.

If you want to know what's the risk of this baby or this child to undergo this procedure to take the cath complications out when, in fact, they were -- maybe they weren't as serious but they outnumbered the number of other complications.

DR. JENKINS: There are a large number and

they are all listed in the Panel Pack in a lot of detail.

DR. WHITE: When you look at the primary safety outcome, it looks like that number may be less than it really was if you count the cath complications into it.

DR. JENKINS: One could have used a different definition That's true.

DR. WHITE: I'm really troubled by the fractures of the device. I'm really troubled by -- I mean, I know that you tell me that it hasn't called a problem but it bothers me that devices are breaking and I want to know what the company is doing about that. Are you making them so they won't break or you want me to keep putting them in to break?

DR. JENKINS: Again, I would like Carol Ryan to come up and talk about that.

MS. RYAN: We're actually -- the device, as I said, is made from MP35n and MP35n is the material that is used in pacemaker leads and pacemaker leads fracture and their fractures are unacceptable and usually have significant clinical sequelae.

The vendor who makes the MP35n for all of us who use MP35n wire in the medical device industry has a significant program that's ongoing to improve the quality of the raw material. We work very closely with them in evaluating each new generation of this material that comes out and implementing it into the product.

Kathy could probably comment to this better than I but an analysis was done of devices made from a variety of generations of this wire. We have shown that there is a statistically significant improvement in the fracture resistance of devices of the recent generation that has been incorporated.

We are continuing currently to evaluate future generations of the material that the vendor has provided us so we expect over time that the fracture rate will only get lower. Maybe Dr. Jenkins can comment on her analysis.

DR. JENKINS: We actually did do an analysis maybe three-quarters of the way through the data that showed you looking at determinants of fracture to figure out if there was specific manufacturing issues,

specific device design issues, or issues related to implantation that could be associated with fracture. It was a little bit of a fishing experiment. We looked at quite a few variables. We actually found three that were significantly related to fractures.

By far and away the most important one is device size as Kim pointed out earlier and as is shown in the fracture section of your Panel Pack whereby larger devices are more fracture prone than smaller ones. That confounder actually confounds a whole lot of other analyses that one might do looking at fractures.

The second one was a specific lot of devices that seemed to have an especially high fracture rate which was part of the impetus for Carol to go back and continue to look at the specific metal that's being used for manufacturing.

The third one was a very broad stroke variable whereby somewhere in the cath reports are follow-up letters. The procedure was described as a difficult device placement leading us to believe that pushing devices around bends in the sheath and things

like that may actually also be part of the determinate of fracture.

That was the most easily avoidable one. But we've done quite a bit to try to look into this. I think as clinicians having watched a large number of patients have fractures in the original Clamshell I cohort that we have also done extensive analyses on, and now quite a few patients experience this later.

We've had an increasing level of comfort around the issue that fractures really are incidental in the vast majority of cases probably because most of them are, in fact, occurring after the devices enthothelialize and are completely covered. Just so you're aware, in the original Clamshell I registry series, there were seven events that were attributed to fractures in the hundreds of events that occurred in that cohort.

Those events were three masses that were associated with a fractured arm friction lesions, three devices that moved, and one arm that actually broke off and impeded in the free wall of the RV. I think we all wish that fractures would just go away

and not keep happening.

Even in the large number of patients in that original series who had fractures, the overall even rate was fairly small and fortunately we just haven't seen it all since 1996 despite screening extensively for them.

DR. WHITE: That's all.

DR. TRACY: Maybe this is a stupid question but why is the arm on the surface and not some place within so that it can't break lose and fly into the free wall or wherever it wants to go?

MS. RYAN: The predecessor, the Clamshell, where a piece of an arm migrated is somewhat of a mystery. It had to have been some sort of manufacturing defect. That device was made under a completely different processing controls than the current product.

The CardioSEAL device actually has each individual coil sewn to the fabric which did not happen with the Clamshell device. The nature of a fatigue fracture once one occurs in an arm, that arm really isn't under any significant stress at that

point. You shouldn't have a fracture at two points. With the coil sewn down there shouldn't be any migration.

DR. TRACY: Thanks.

Do any of the panel members have any additional questions they would like to ask the sponsor?

Dr. Williams.

DR. WILLIAMS: Just one very brief one. Under the contraindications, I think it would be reasonable to say the anatomy in which the CardioSEAL size required or position would interfere with intracardiac or intravascular structures because of the issue that you do select defects in which the position of the device would not interfere. I would put that specifically on the contraindications.

DR. TRACY: Any other members of the panel?

DR. LASKEY: Did I understand you correctly to say that you have not had a fracture since 1996?

DR. JENKINS: No. We haven't had any adverse consequences of a fracture in the entire high risk cohort.

DR. LASKEY: Just for my own clarification, two hours ago I asked the question who should this not be put in. I got a rather cursory answer which wasn't helpful. Now I come away hearing that there are defects where it shouldn't be approached.

Can you just give me a Reader's Digest summary of who this is appropriate for vis-a-vis which patients are not surgical candidates which, of course, you have in your IFU, but more specifically the anatomic subset which is not likely to do well with this procedure.

DR. JENKINS: That are not likely to do well with the cath procedure? Is that what you're asking? I think that the subgroup of patients that are not likely to do well with this procedure would include patients with VSDs in locations that are within 5 mm of semilunar or AV valves or valve apparatus: Or patients who are too small to have placement of 10 French catheters in their vasculature.

DR. LASKEY: And the postero-septal defects that are perhaps a little too close to the base and to the insertion of tricuspid leaflets. I took something

away from that discussion as perhaps being not as ideal a situation as other regions.

DR. JENKINS: I'm going to ask Dr. Lock to answer this question.

DR. LASKEY: Over the last couple of hours the answer to that question changed.

DR. WILLIAMS: My interpretation of his answer is it's harder than the other ones but it may be the only alternative. The question we have to determine is whether in hands other than Dr. Lock's it is likely to be successful.

DR. LASKEY: And that summarizes my concern. Dr. White, thank you for getting my adrenaline going again. You guys are experts beyond two standard deviations of the average interventional cardiologist.

If you expect this technology and capability to penetrate into the lower levels or the lower echelons of this profession, I don't have any desire to do this. I'm not even sure I could but if I wanted to.

Frankly, I'm intimidated and I've been doing intervention in sick people for 20 odd years but this

is a whole other order of magnitude here. I don't know if I speak for the profession or just for myself, but I get the feeling that there is a body of knowledge here and the level of expertise which desperately needs to see the light of day in order to make informed judgements about who should get this.

It has to be done in the context of expert surgery, expert anesthesia, a whole group of experts which is to be found only in 30 centers, did you say?

This all started out with my unease as the afternoon developed about, well, it's going to work better in some than in others. I think that's not clear from this material. I think users other than you need to know what to expect.

DR. ZAHKA: I would agree with you but disagree in the sense that the community of interventional pediatric cardiology is a very broad one. We heard about one center who has done three successful ones. I think that Dr. Lock is probably very articulate, because he is very articulate, at telling what are the tricks of the trade.

There's a great body of experience in

pediatric interventional cardiology that I think can be brought to bear on this so that the situation is perhaps not as bleak as it might seem from the adult world.

DR. LOCK: This is probably gratuitous and unnecessary, but there was a period of time 20 years ago where there was really only one place in the country that did hypoblast surgery. There was a period of time when really it was thought that only a few places could successfully perform that procedure.

It did take five or 10 or 15 years for that operation to become a national standard. Now, it isn't done in every center in the country but it is done in quite a few centers around the country. I expect exactly the same transition will happen with this kind of complicated intervention in children.

Therewillbemore complicated interventions in children like this that won't be done in two or three hundred places but will be done in 50 or 80 or 30 or 20 very successfully as time goes on.

DR. TRACY: I think there is some difficulty because the only real concrete thing here is the death

rate which was about 7 percent. But you're talking about a procedure that has a 99 percent adverse event rate which anybody could go out and say, "I'm going to do a procedure now because there's almost a 100 percent chance that something will go wrong."

I think that in the education of the physicians, all of these intangible things really have to be conveyed very clearly. Who best is this suited for? Who is this not suited for? What are the things that we have learned from our experience?

That kind of information has to be passed along because not even well-trained interventional cardiologists will have had that much experience doing transeptals. There's about a 1,000 pitfalls in this procedure where things can go wrong.

Each of those steps require some training. It's not everybody who should be taking on this type of procedure. I think that is the unease that many people feel about this procedure.

Dr. Williams.

DR. WILLIAMS: This is getting a little bit more into the domain of discussion than question so

I'll include Dr. Lock in this discussion point.

It seems to me those of us who have looked at surgical outcome relative to institutional and operator volume know that in general there is a difference between large and small but there are many, many exceptions that have to do with institutional organization accumulation of learning curve.

One option that we would have is to try to put some very arbitrary volume limits on this. But I wonder whether in the end more patients would be served if we put very, very heavy educational requirements' on the team and institutional record keeping. And if there were very, very careful post-market surveillance and that perhaps taking the most difficult type of VSD which would be the posterior muscular VSD and say in order to qualify to do that type of VSD, that institution would have to have both efficacy and safety record equivalent to Boston Children's Hospital. Now, that would be tough but it would be -- you know, you could earn your --

DR. LOCK: I intend to make it impossible.

DR. WILLIAMS: Of course it would. At least

equivalent to the average of the institutions of the group which would be a lower target. The indications to this, who is going to do it, is whether you belong to the tribe that believes in no stone unturned in a dying patient, or you belong to the tribe that says above all do no harm.

That's a matter of philosophy. That is also a matter of what your other alternatives are. It is an imponderable when we talk about different institutions because the resources of those institutions are different and every patient is like a snowflake. They are different.

I personally would feel more comfortable saying go ahead, but putting these stringent requirements on education of the team on post-market surveillance and letting that be as close as we can get to what is the right thing.

MR. DILLARD: Dr. Tracy, Jim Dillard. Just a point of reminder for the advisory panel is that we are sort of skirting that line and going over and coming back a little bit in terms of practice of medicine and just to remind you that we really don't

get involved with a lot of the practice of medicine.

I think Dr. Williams brought it back a little bit to say what some of those training requirements might be which is something we'll work obviously very closely with the company on.

A number of these in terms of who's going to do it and how many you have to do, I think, really gets in much more to the practice of medicine and something that I think their profession needs to regulate a lot more than the agency is going to. I just wanted to remind everyone.

DR. TRACY: I would agree with that except to the extent that this is a team approach and I think that part of the physician training -- what I would take from this as a concrete thing is part of the physician training has to include all the different pieces of the team that are going to be present or potentially present including the cardiac surgery team.

DR. HOPKINS: I just want to say thank you. I'm just about ready to raise that issue. We're talking about 57 patients here in four years. I mean,

we can get so stringent that no patient ever -- the patients are out there dying because they don't have access to this device because we've created this philosophically stringent.

When I first went to medical school at Duke, the only place in North Carolina that did aneurism surgery was Mr. Duke's hospital and now it's probably done in every hospital that has 50 beds or more.

I think we are getting way afield of labeling and indications and what is intended here which is moving a device that has been remarkably effective in a very tough set of patients from a humanitarian device.to a premarket approval. All of the other stuff that sort of in the last 20 minutes has been very philosophical but I don't think has anything to do with this.

I agree with requesting of the company to do rigorous training but that's different than limiting access of the device to some subset of a subset of a subset.

DR. TRACY : I think there is one more question from the panel.

DR. WITTES: I feel like I'm in Never Never Land. I don't understand. I need to hear some numbers about what the mortality would have been. What we're hearing is this is remarkably effective, what the mortality would have been had the device not been here.

What would the shift have been in the clinical efficacy? I worry exactly as Dr. Laskey does about whether -- how much of this is regression to the mean, It may be none of it is but I need to hear you tell me that if I had 57 patients and I didn't give them this device, X number would die within six months and nobody would shift over in the improvement. Otherwise, I'm feeling like it's a matter of faith.

DR. JENKINS: I think we should have John answer that.

Fifty-seven patients, John. Half had failed VSD surgery elsewhere. The other half had passed a peer review whereby a surgeon, maybe yourself, maybe someone else, and a cardiologist had declared that the VSD would have been very difficult to approach in the operating room

DR. MAYER: Well, I guess what was running through my mind there is to give you some context about what's the natural history. Forget surgeon, cardiologist, or anybody.

The natural history of patients with large ventricular septal defects, large defined as having a big left-to-right shunt is as follows. There's a large number of those patients who will die from congestive heart failure.

There's a huge volume load placed on the heart. There's three times as much blood going through the lungs every minute as go through the body. Those patients are highly susceptible to pulmonary infections.

A virus that you or I would throw off will kill those children. You know, they can't grow because they are wasting so much metabolic energy pumping all that extra blood around that they can't devote energy to getting bigger like babies are supposed to get.

And there are a significant number of those patients who have elevated pulmonary blood flow so a

lot of extra blood going through the lungs at very high pressure who will then progress to develop what is called pulmonary vascular obstructive disease. The natural history of an untreated large ventricular septaldefect inchildrenis particularly unfavorable.

That's why 40 years ago when cardiac surgery started, cardiologists were willing to send patients to surgery even who had surgically easily accessible VSDs because the mortality rate was 25 percent with an operation, but it was still better than what the natural history was.

So that's the sort of floor context. If we take the subset of patients who had a pulmonary artery band which is a palliative procedure that you can do that will limit the amount of pulmonary blood flow drops the pulmonary artery pressure down strained to the band, keeps them from getting pulmonary vascular obstructive disease, and we don't have an adjustable band.

What might work pretty well for a baby age six months, by the time that child is three or four years old, they're not going to have left-to-right

shunt. They're going to have right-to-left shunt.

They are going to be blue. They are going to be exercise limited. They are going to be at risk for strokes and all the things that kids with cyanotic heart disease get. That's another subset of what can happen.

Certainly the patients who went to surgery to have a VSD closed in whom it didn't work -- the surgeon couldn't get access to it because it was in a difficult location or whatever other reasons there might be, complicated anatomy -- those patients presumably went to surgery because there was an indication for doing an operation.

From my standpoint, and I guess I would hearken back to the practice of medicine question versus what is the device related issue, at least in our place this has been a pretty rigorous process because you have to get a surgeon and a cardiologist both to agree that this is something that is the best course of action, least risk path of treatment for this particular patient. It's really done on a case-by-case basis. That's always informed by a whole

variety of personal experience, literature experience, so forth.

I guess from my perspective, and having been a reviewer on a number of these cases as they have come along and, to be honest with you, having kicked some out saying, "I think I can close that hole," ones that came through, and some of which I actually did operate on and close the whole, I think all of those factors make it, I think, 'extremely difficult to construct a control group.

In the same way that there were difficulties with having what is clearly a multiple clinical presentation set of patients, and trying to figure out a scale how you deal with the banded patients who then got their device closed and then had their pulmonary band taken off, and construct a scale that is also consistent with the patient who had multiple ventricular septal defects and hadn't been banded and had one or more VSDs closed by device, I mean, it inherently is just a complicated set of patients.

I think that is the problem with -- I mean, I understand from a statistical standpoint why one

would like really to have a comparable group of patients.

DR. WITTES: Well, I'm not even asking that much. I'm asking for a number. I'm hearing essentially 11 percent, six-month mortality in this group is what there is. Is that right?

DR. JENKINS: Four patients died and one died because of the catheterization for a mortality of 1.7 percent. One patient out of 58 patients died directly due to the procedure.

DR. WITTES: But, to me, it's still four out of 57. However --.

DR. LOCK: Can I interrupt for a second? The other three patients who died died from their underlying disease.

DR. WITTES: That's what I'm asking. What percentage of people -- if you had 57 --

DR. LOCK: Those were the patients who weren't made better necessarily. For all the patients who were made better, it improved their overall survival.

I don't know how to put this but there have

probably been 10 patients who were in one fashion or another didn't come for the device and I know of three who died waiting. This is a very difficult patient population to get mortality rates on. If we gave you a number, it would be arbitrary.

DR. WITTES: I don't care if it has a 20 percent spread. I just want to know --

DR. JENKINS: The old-fashioned number that is widely taught to cardiologists was that there was a 20 percent of patients with this disease that didn't come off pump.

I actually tried to track down where that number came from because it's been widely quoted. I had trouble actually finding it so I tend not to give information I can't find.

It's wide quoted that the mortality rate of not coming off pump, if you take somebody with multiple VSDs to the OR and you don't close all of them, it's 20 percent.

DR. TRACY: Okay. I think I'm going to ask Mr. Morton and Mr. Dacey if they have any additional questions. I know there are many sort of unanswered

questions here but unless there is something very specific that can be answered by the sponsor, I think we need to move on to the FDA questions.

Can I ask the sponsor to stand back and we'll move on to the FDA questions if somebody can flash those back up.

The first question is dealing with the complexity of the VSD in patients entered in this registry has been defined variously as VSD not accessible to closure through an atria1 or aortic approach associated with other cardiac pathology patients with single or multiple muscular septal defects or simply patients at high risk for surgery.

Question la. Based on the information provided, please discuss the description of "complex VSD" as the defining indication for use of the CardioSEAL for VSD closure.

I think in the indication in Section 2, I think it is, the indication is the CardioSEAL inclusion system is for use in patients with a complex ventricular septal defect of a significant size to warrant closure, but that based on location cannot be

closed with standard trans-atria1 or trans-arterial approaches, which is a little bit more simplistic than what Dr. Mayer detailed or than the patients that are actually included in this study.

I would suggest perhaps using something that is a little bit more reflective of Dr. Mayer's, I believe, sixth slide that listed the definition of high risk which included low probability of satisfactory surgical exposure, left ventriculotomy, excessive right ventriculotomy, high probability of residual VSD, failed previous VSD, multiple apical and/or anterior muscular VSDs, and posterior apical VSD covered by trabeculae.

I think maybe more specifically stating in the indications the actual patients that were included would be helpful.

MR. DILLARD: Can I ask -- excuse me. Jim Dillard. Can I ask a real quick question, which is is that all encompassing? I mean, are we even missing anything with that that may be important if we don't have the general statement. That would be my only question.

DR. SKORTON: I think there were a couple of other things that will be in the transcript from Dr. Lock's remarks that should be folded into there too about post-infarction VSDs and posterior versus anterior. I think the sense of what she brought up is right.

DR. WILLIAMS: But the indications, I think, are, as you say, are good. The contraindications may indicate the post-infarction VSD. I think defects that interfere with the valve would be in the contraindications. It happens that most of those defects are accessible so I think that is the correct -- you have the correct definition for indications.

DR. WHITE: I don't think we saw any data about contraindications. Did we? I mean, I think we just don't want to list it as an indication but I don't think we saw any data regarding the contraindication.

DR. TRACY: I think the contraindications are what are listed here, the obvious things on clots, etc. I believe Dr. Lock's comments have to be reflected somewhere in there. I don't know that I

would put them down as contraindications but perhaps data is less than optimal results or some type of qualitative statements could be made regarding that.

Question lb. In the absence of a control group, please discuss how to evaluate the safety and effectiveness of the CardioSEAL device.

I think you've heard the discussion. There is no control group. It's what it is in a very high-risk patient population.

Question 2. Does the use of the Clinical Status Scale allow for a clinically meaningful assessment of effectiveness for the device?

Again, I think you've heard the discussion about that. It's difficult to get a handle on it but, again, it is the definition that was used. There are data here that are useful. Any other comments specifically on that?

DR. WHITE: I'm just troubled by the fact that there is no composite endpoint that should be -- 1 mean, I'm not asking for a randomized trial there. I'm asking for a very conventional way that we assess outcomes and this didn't do that.

DR. WILLIAMS: I would suggest that this isn't a conventional group and that's why we can't because there really is no composite. They were asked to do it and they did the best that they could under the circumstances.

In truth, to mix the indications of left-to-right shunt in more complex right-to-left shunts is probably meaningless and I think they made as good an attempt as they can possible do.

DR. WHITE: I don't think that's true. I think given the data here I could tell you how many people had the procedure done, a technically successful procedure, and had a major complication.

I mean, it's just a matter of how you measure the data and whether you accept or whether you require the fact that success happened without or with a major complication and whether you're willing to let that happen.

DR. WILLIAMS: You could look at technical success with closing the hole but if the issue is the effect on the patient's course, then you cannot mix those two things together, I don't think.

DR. SKORTON: I think the answer to No. 3 sort of resolves the issue of No. 2.

DR. TRACY: Question 3. Based on the data provided and your comments regarding questions 1 and 2, please discuss whether these data provide reasonable assurance of safety and effectiveness.

I think that's obviously what we're struggling with. This is not a safe group of people to be working. However, it does appear to be a viable option for treatment in this very high-risk group of patients.

DR. WHITE: I think that is the reason for an HDE.

DR. TRACY: Anything else troubling? Ms. Moynahan seems troubled by that. I'm not sure why.

DR. JENKINS: It's kind of the pivotal question and I think a couple of the comments might help;

What do you think, Jim?

MR. DILLARD: Well, I mean, I think we heard Dr. White have perhaps a little bit different perception. There's not a right or wrong answer even

to the question I think that you're raising, which is how do you differentiate what is an HDE versus what is a PMA.

Let me try to boil it down into something pretty simple which is this product is on the market at 30 institutions because the company has demonstrated that there is reasonable assurance of safety and that there is probable benefit.

Now today what we're saying is the data that we're looking at today pushes over the line from reasonable assurance of safety and probable benefit to reasonable assurance of safety and reasonable assurance of effectiveness.

I think that is perhaps the pivotal question here today which is the data now presented here with 57 patients enough to say there is reasonable assurance of effectiveness.

At the time we looked at the HDE a lot of that information wasn't complete. Safety seemed to be there. Is this really enough to judge effectiveness of the product for this patient population.

DR. HOPKINS: I would have to say for me the

answer to that is yes, that there is reasonable assurance and that one suppose. I can actually give you my answer to your question because I'm not bound by the data. As a surgeon who would have to make a decision whether to operate on these patients, I would typically quote these parents 25 to 50 percent mortality so if that gives you a figure compare.

DR. WITTES: Yes, that's the sort of figure I needed.

DR. WHITE: But the question then, Dr. Hopkins, is what has persuaded you that they need more than an HDE, you know, if this device isn't ready for prime time? I'm not arguing that 'this device shouldn't be used and I'm not arguing that you have a need for this in your patients. What I'm suggesting is I haven't been convinced that there is a need more than a HDE.

DR. HOPKINS: I think Jim Lock actually referred to it. The actual dynamics of 'what happens with these patients is that if you don't have such a device available, you either get pushed towards surgery or the patient sits waiting for resolution in

terms of referral to a center that does have this available.

DR. WHITE: This device is available in 32 centers of which we received no data. We don't know how those people performed. One of my concerns is that this all-star group here who had significant problems is not going to be translatable to those other 32.

DR. HOPKINS: Yes, I share those concerns. I think in the questions to come is where I would recommend that we resolve that. That is, in the training issues and then perhaps the post-release surveillance issues rather than in the PMA.

DR. TRACY: So I'm going to leave the answer as being within this very small group there is some assurance of the effectiveness of this procedure as well as the safety.

Moving on to the training program. The summary of that is in Section 5 of the Panel Packet.

Question 4a. Please discuss any improvements that could be made to the training program.

I think it's just a very, very difficult

thing to come up with a training program that will reflect getting trained as a superb and highly talentedinterventional cardiologist who has access to the world's best cardiac surgeons in the presence of a highly trained and expert group of cardiac anesthesiologists, but somehow you have to convey that all of those pieces are needed in this training program.

I think to reflect all of our concerns, the training has to somehow haul in all these people and get them to understand the seriousness of the clinical situation. I don't know exactly what to do with the fact that in this protocol a group decision was made between surgery and cardiology as to whether the person was a candidate for this device.

Is that something that we would recommend that that discussion be held on each individual patient, or is this the decision that the cardiologist is going to make and then the surgeon is going to have to live with? I don't know. I'm asking the surgeons whether they would like that.

DR. HOPKINS: I would have to say the nature

of the practice of pediatric and adult cardiac surgery is actually very different in terms of the dynamics between the cardiologist and the cardiac surgeon.

I would think that in every center where I have ever been and have ever visited, the decision on therapy, particularly invasive therapy for pediatric patients, is done in concert and as a group and rarely done in the same fashion that adult decisions are made where a single cardiologist makes a decision and refers the patient to a single cardiac surgeon. I think the actual general dynamics of the clinical care model is so different that it takes care of that.

DR. WILLIAMS: I would add in terms of the training, I certainly agree with what Dr. Hopkins said. I think in terms of training requirements I would specify that there be a locus of responsibility, echo, anesthesia, surgery, and cath. They meet as a team, and that the learning curve be concentrated in those individuals because it's terribly important starting out to accumulate the learning curve under one umbrella.

DR. SKORTON: I have a question about that

from doing this a few times. It's one thing to suggest that a person who does that has no teeth whatsoever. Once the thing is marketed you can do anything you want. You can put it in the very first person you see.

A question for you. If we bought into Dr. William's ideas is it practical or doable to insist that before being given access to the device someone go through a particular training program? Because if it is or it isn't, that would have a big effect on whether this is a practical idea or not.

MR. DILLARD: Jim Dillard. I think that one of the responsibilities on the part of the agency is to certainly work directly with the sponsor to try to come up with a reasonable training program.

I think our first approach to that is much of what you have already discussed here which is what have the world's experts learned in terms of the initial clinical approaches as well as what the data says and how do we translate that then to the general teams that might be at the other institutions.

I think we are at maybe a little bit of an

advantage than we usually are at this stage because perhaps they have already done it 29 more times than they would have otherwise done because they have been through that training and there are other institutions based on the HDE.

They probably learned even a lot more than the companies who would be sitting before us here saying, "We've only trained a couple three centers that we've done the clinical study on."

I think actually the sponsor may have some additional comments on that, No. 1, but 'beyond that, No. 2, we would work very closely with them, we would. learn from what their experience is, and that would be part of our conditions of approval to come up with a training program that is satisfactory to the agency.

DR. WHITE: If we simply required that a physician be proctored for three cases, which is common in many devices and other things, you could pocket veto this PMA because there aren't enough cases out there for the physicians to be proctored for three each. I think that is one of the big issues here. Who is going to save three of these up for a proctor?

DR. TRACY: However; there are 30 centers that somehow have managed to get the device up and running so there is a way to do this.

I was just concerned because the verification form only deals with the interventional cardiologist. There must be something, as Mr. Dillard says, that the company and the mentors already know that have permitted this thing to expand out to a number of centers.

DR. WHITE: I'd be careful about what you think the 32 centers are doing. I think we haven't seen any data regarding that.

DR. WILLIAMS: But I'd also be careful -- I'm not myself interested so much in pocket veto. I'm more interested in helping the company set out the conditions that will end up with the best result because I think this is something that should be propagated safely.

DR. HOPKINS: I think the sense is that the group wants some rigor in the training. Ultimately in the latter questions of the post-market evaluation we are going to deal with some of those issues.

DR. TRACY: Okay. 4b. More than one device was placed in 26 patients. Please discuss training issues regarding the placement of multiple devices in a single patient.

Obviously, the more you do the more complex it is. The more training you need, the more sponsoring you need.

DR. WILLIAMS: But you might not always know when you're going to have to do that so I don't know that you can necessarily in‘advance decide that.

DR. WHITE: Remember that two-thirds of these procedures had two guys working. You talked about your anesthesiologist and other people but this is somebody pulling on this wire and somebody pulling on that wire and they are a team. This isn't what one good guy can go do. This is a real tour de force, I think, to do these well.

DR. TRACY: Again, emphasis on the team approach.

Product labeling and that information is contained in Section 2.

5a. Please comment on the INDICATIONS FOR

USE section as to whether it identifies the appropriate patient populations for treatment with this device.

I think we already discussed that.

5b. Please comment on the CONTRAINDICATIONS section as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.

The only thing that I would add there is that the thrombus that's mentioned is in various vessels but if you have somebody with a clot in the left atrium, you probably shouldn't be doing this either.

I think that -- 1 had written in my notes posterior muscular defects are at higher risk. I don't know if this necessarily rises to the level of contraindication but probably comes somewhere down in the warning section to just state that.

DR. WILLIAMS: But position that would interfere with the function of a valve, any of the cardiac valves, would be in addition.

DR. TRACY: Right. One of the

contraindications that is already listed is anatomy in which the CardioSEAL size required would interfere with other intracardiac or intravascular structure such as valves or pulmonary veins.

DR. WILLIAMS: That only says size. It doesn't say position so I would say size or position,

DR. TRACY: Okay. I think we had discussed pulmonary veins as not appropriate to this particular application so we would probably take that wording out.

Any other specifics on contraindications?

5c. Please comment on the WARNING/PRECAUTIONS section as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

I think this would likely be where we would add those other anatomic caveats.

5d. Please comment on the OPERATOR'S INSTRUCTIONS as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

I read through this and thought that it was

quite good but a picture is worth a thousand words and I think this is where the education would come in.

5e. Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.

Any additional comments?

Post-market evaluation. Question 6. Based on the clinical data provided in the Panel Package, do you believe that additional follow-up data or post-market studies are necessary to evaluate the chronic effects of the implantation of the CardioSEAL device? If so, how long should patients be followed and what endpoints and adverse events should be measured?

This is extraordinarily hard to come up with something like that in a population that is so limited to start out with. The numbers are so small to start out with. I think to recommend in a group of patients that are going to die of their underlying cardiac condition or other conditions anyway, it's extremely difficult to come up with a concrete recommendation on this.

I personally think that -- I hate to use the word registry but I personally think that something of that ilk is probably the right way to do this but I don't know. Do any of the other panel members have better comments than mine?

Dr. Wittes.

DR. WITTES: Well, can we take up Dr. White's suggestion that there are 29 centers out there with presumably data. Can those data be looked at? Is that legal? I mean, that actually would be part of the training. If those centers are having trouble, there may be information in the data that is already there.

DR. HOPKINS: There's really two questions that are being asked here, and that is the outcome of the individual patient in which that is probably known within six months of the implantation of the device or certainly within 12 months.

The other is the issue of the center efficacy as opposed to the patient based efficacy. That is sort of more of a registry, I think, type of approach. Maybe the follow-up should be suggested to

be 12 months for the individual patient and a number picked for a center.

The center has to maintain appropriate records and report them to the company and ultimately thus to the FDA for 15 or 20. Just pick a number. You are really measuring two completely different things here.

MR. DILLARD: I might make just a real quick comment and then the sponsor may just want to address it, too. I'm not sure, Dr. Wittes, whether or not those other institutions really have "data" per se.

They may have information and they might come up and even say they could go so far as to say whether or not they actually have some mortality information on perhaps what I would expect to be a very small number of patients even at some of those other centers.

I don't know how much we will actually glean from the knowledge of what we may know up to this point in time, but I think what might be important is if you are sitting here today, and I heard some issues that came up about what might be nice to know even in

the future if we come back three, four, five years from now, what is going to be important to be able to say about the CardioSEAL device for VSDs, especially complicated VSDs, that U.S. clinicians might want to know about, about how the product is doing and how would we assess it in a little bit longer term. Would that then be important to the post-market period to look at.

DR. TRACY: Dr. Skorton.

DR. SKORTON: I think it would be and I wonder in the interest of efficiency when I make the motion if I could present some specific ideas how to do that in the motion.

DR. TRACY: Do you want to wait until we get to the --

DR. SKORTON: Instead of discussing it twice because I have a motion.

DR. TRACY: That's fine. Okay. I think that is all of the FDA questions unless the FDA has any additional questions at this time or comments.

MR. DILLARD: No, thank you.

DR. TRACY: Does the sponsor have any

additional comments they would like to make at this time?

Mr. Morton, Mr. Dacey, any additional questions or comments?

Okay. Dr. Skorton, would you like to make --

MS. MOYNAHAN: You need to do open public hearing.

DR. TRACY: Oh, I apologize. Is there any member of the public here present who would like to make any comments at this point at an open public hearing?

If not, I'll close the open public hearing. Sorry I forgot that.

MS. MOYNAHAN: In case any of you forgot since this morning, I'll read them again.

The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990 allows the FDA to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the agency.

The PMA must stand on its own merits and your recommendation must be supported by the safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined.in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions on intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended use as conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows:

(1) Approval if there are no conditions attached.

(2) Approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions such as physician or patient education, labeling changes, or further analysis of existing data. Prior to voting all of the conditions

should be discussed by the panel.

(3) Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. TRACY: Right. At this point, Dr. Skorton, I'll ask if you have a motion to make regarding this application.

DR. SKORTON: Yes. I move that the device be approvable with conditions and then, at the appropriate time, I have four conditions to suggest.

DR. TRACY: Go ahead.

DR. SKORTON: We have to have a second first to the motion.

DR. WILLIAMS: Second.

DR. SKORTON: Okay. My first condition is

that I believe there should be mandatory post-market studies for five years, that the studies should be annually, that a patient should annually get fluoroscopy and echocardiography, and that the six endpoints that should be looked for are the status of the device arms where fractures have occurred, thrombosis, global and regional ventricular function, endocarditis, evidence of ventricular arrhythmias or conduction disturbances, and evidence of residual shunt.

DR. HOPKINS: Could I address the issue of fluoroscopy? I don't think the arm fractures as we know it are really that important late because while it sounds like a bad engineering thing to have happen, actually late the device is locked in by the fibrous ingrowth.

From a practical standpoint an echo can be done in multiple outpatient facilities where fluro requires bringing them in to the hospital. Adding fluro adds a real increment of difficulty in the follow-up of these patients. I'm not so sure it's as important as the other criteria that you mentioned.

DR. SKORTON: I don't feel strongly about it but I'm responding to what I heard the investigator say was the way they discovered the fractures.. Since there will be new ones put in and since I thought I heard the engineering aspect of the sponsor say there was a little bit of a moving target in terms of the materials they were made out of and the way they were constructed, I'm uncomfortable not following up in some fashion.

If there is something that can be done besides fluoroscopy to look for arm fractures, that's great with me but I don't think echo would be the right way to do it.

DR. WILLIAMS: Would it be okay just to not specify the technique but to say what is best in that institution because even fluro if it's not done by the same person might not be as adequate.

DR. HOPKINS: I think mandating echo annually for five years is not inappropriate.

DR. SKORTON: Something, however, to look at the presence and outcome of device fractures because there were 16 percent fractures. Even though I agree

with what you said from the data we've seen here, this is now going to be open to a much broader denominator and I'm just uncomfortable. Maybe the device fracture rate is a lot lower but I don't know that.

DR. HOPKINS: But even if it is, I think the point is the arms could be absorbable and the ultimate outcome once it's locked in doesn't really matter.

DR. WHITE: I don't think you know that it's locked in. I think you -- I mean, I worry about that. I think we wouldn't be considering any device that had a one in five chance of breaking or a one in seven chance of breaking for most other applications.

I think it's a little cavalier anyway. This is an opportunity if we're going to do this to at least track it and at the end of five years be able to say whether any came out or not.

DR. HOPKINS: I was just pointing out that fluoroscopy is much more of an impediment to the mandated follow-up that you are suggesting.

DR. SKORTON: Maybe it's a certain kind of x-ray. I don't know, but I would ask that the condition be discussed with the sponsor and the

investigators who have collected pivotal data.

DR. WHITE: An impediment to the patient to come back, you mean?

DR. HOPKINS: Yes.

DR. WHITE: I mean, these are kids that are looking at getting transplanted. I mean, this is serious stuff. I mean, I don't think that's a big deal.

DR. HOPKINS: If they're out five years, they are doing pretty well.

DR. TRACY: Mr. Morton.

MR. MORTON: Regarding the diagnostic that's used and the effect it might have on the patient, might we not ask what is the result of the fracture and maybe look for those sorts of things rather than look for the fracture itself? We examine for fractures and we leave that up to the sponsor to get back.

DR. TRACY: I think, though, that the point regarding that is that we don't know what the consequences of the fractures are., We don't know if that later on that this will lead to some kind of an

edge that can create even a rupture in the endothelialized surface that could lead to thrombus formation. We don't know.

There are other devices that have had fracture type of instances with them and they are followed by cardiac fluoroscopy. It is cumbersome but we do this. I don't think it's unreasonable in a device that has a 20 percent problem rate to request that fluro be done.

I personally would support that. I'm not committed to saying that they have to do fluro but I do think that is something that we don't know where that's going to go.

DR. SKORTON: Would you be more comfortable with, say, fluoroscopy or an equivalent technique?

DR. TRACY: Okay. So then your condition is that --

DR. WHITE: I'm running through those equivalent techniques here. There's fluoroscopy and fluoroscopy and fluoroscopy.

DR. TRACY: Well, you could get a flat PA and lateral. If you saw a big thing sticking off of

it, you would know there was a big thing sticking off of it.

DR. SKORTON: I heard the investigator say that they discovered some of the fractures with chest x-ray and some with fluoroscopy. I would be comfortable understanding that this is only advice for the agency and for the agency to work with the sponsor.

DR. WHITE: I've had the experience of looking at the fractures for the valves. The York-Shileys and the chest x-ray is not of the same -- I mean, you miss the little things with the chest x-ray so it's an underestimation, whereas with the fluro, and even sometimes sine is necessary depending on the thickness of the wires in order to be able to see that break. I think that it's not the same.

DR. TRACY : All right. Then for this particular condition, shall we vote on this particular condition for a five-year follow-up with the details as stated by Dr. Skorton.

MR. DILLARD: Jim Dillard. Just one quick question. I thought I heard the answer, but I'm not

sure. It sounds like you're advocating, in addition to potentially following the cohort of patients that we currently have, you're talking about new patients that otherwise would receive the device? Is that correct?

DR. WHITE: Yes, that's correct.

DR. TRACY: So for new patients also. All in favor?

MS. MOYNAHAN: Ten in favor.

DR. TRACY : So that's unanimous. Any additional conditions?

DR. WHITE: Yes. I don't know exactly how to state it without taking three hours to do it but all this stuff that Dr. Williams said about augmented training procedures, something that could be boiled down by the agency and the sponsor I think needs to be added as a condition.

DR. TRACY: Okay. I won't even attempt to summarize the three hour discussion but some type of augmented training as a condition. All those in favor?

MS. MOYNAHAN: That's unanimous at 10.

DR. TRACY: Any additional conditions?

DR. SKORTON: I guess just one more, and that is as one condition all the labeling clarifications that we mentioned under indications, warnings, and so on, all those together to be made as a condition.

DR. TRACY: Okay. So the third condition is verification of the changes in the labeling that we've suggested. All in favor?

MS. MOYNAHAN: Okay. That's 10.

DR. TRACY: All right then. The motion has been made that this is approvable with conditions. The conditions have been stated and voted on. At this point let's vote on the major motion approvable with conditions. All in favor?

MS. MOYNAHAN: Is your hand up, Dr. White?

DR. WHITE: No, it's not.

MS. MOYNAHAN: Nine.

DR. TRACY: Opposed? Can I then ask each of the panel members to individually state what your vote was and the basis for your vote.

We'll start with you, Dr. White.

DR. WHITE: Well, I think I was the only one who thought this was not approvable. It's not because' I don't think the device is good or doesn't have a good use and it isn't valuable, but I was not convinced that it needs to be more than an HDE.

The administrative inconvenience of HDE to me doesn't justify the release of this device. I think we have a lot of chance to do a lot of harm here without doing a lot of good. I think the efficacy endpoint really was not -- didn't satisfy me.

I think the safety is questionable. I would have a lot of concern being on record for a device that has this fracture rate and approving that.

DR. TRACY: Dr. Williams.

DR. WILLIAMS: Well, from my clinical experience, I believe this is a group that has few other options. I believe that they have demonstrated reasonable efficacy and safety relative to what I understand the natural history of this disease to be. I believe that our conditions have set forth protections for the significant multiple operator dependence for this particular type of device

placement.

DR. TRACY: Dr. Skorton.

DR. SKORTON: I voted for approval for two reasons. One is that I've had the experience of not knowing what to do with a handful of people like this. It's just been a handful and I've become more convinced today that the surgical options are quite limited.

Secondly, I believe, although I do agree absolutely with safety concerns, which is why I brought up one of the conditions, I think this is not going to be one of.those procedures that people are going to be running to do.

I think it will be somewhat self-correcting because of the very difficult nature of it. I have confidence that the agency before issuing an approval, if it chooses to, will develop some sort of training and surveillance system that will make me more comfortable.

DR. TRACY: Dr. Zahka.

DR. ZAHKA: I voted for approval because I think this is a difficult group of patients who need

this kind of approach. After I convinced myself that there would not be slippage of an approach to patients who, in fact, would be better done surgically. That was a major concern for me. I did come away convinced that this device would, in fact, find it's way only into patients for whom surgery was not a good option.

DR. TRACY: Dr. Hopkins.

DR. HOPKINS: I voted for it for the reasons that the two folks preceding me mentioned. I actually think it will increase the efficacy or the outcomes. Also for the surgical patients because of the kinds of conversations that the clinicians will have by having this device availability will foster the team approach.

DR. TRACY: Dr. Aziz.

DR. AZIZ: Well, I voted for it because I think this may be an option for a very difficult group of patients who really don't have much else even though I think I echo Dr. White's concerns that it does have a lot of questionable issues.

DR. TRACY: Dr. Laskey.

DR. LASKEY: Well, I voted for approval as

well with the qualifications noted but I'm terribly uneasy because this is the first time I've certainly reviewed anything which was not rigorously controlled.

I think that many of us were responding emotionally and overreaching and, yes, this is a desperate population and, yes, it is nice to have another option and, yes, this probably will be used correctly by a small handful.

I think that ultimately came down to saying yea rather than nay. I just don't see 'hundreds of people using this device. I see it centrally controlled in expert hands. I hope it is as efficacious as we all hope.

DR. TRACY: Dr. McDaniel.

DR. McDANIEL: I voted to approve with conditions as stated for the same reasons as my colleagues. I think that it's a limited number of patients. It will offer something to some children that may be expiring in institutions without the ability to do this. It's critical that the FDA follow some of our suggestions in terms of the training, but

agree that it's not going to be done in a tremendous number of patients.

DR. TRACY: Dr. Wittes.

DR. WITTES: I voted yes for much the same reason. I became convinced that this is a desperate group that needs something. I wish there had been some more control data of one kind or another.

DR. TRACY: Dr. Crittenden.

DR. CRITTENDEN: I voted for approval with conditions. Again, I share a lot of the concerns voiced by previous panel members but this is a desperate group of patients who have few options so I think we've done the right thing.

DR. TRACY: Mr. Morton, any comments?

Mr. Dillard?

MR. DILLARD: Yes. I would just like to thank not only the two sponsors today but certainly this group of individuals who came in mostly for this day. There will be a few that I think will be back tomorrow, but I appreciate you all coming in today and taking a look at these occluder devices with us. Appreciate it.

DR. TRACY : Thank you, everybody. I'll adjourned this meeting.

(Whereupon, at 6:00 p.m. the meeting was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of Circulatory System Devices Panel Meeting

Before: DHHS/FDA/CDRH

Date: September 10, 2001

Place: Gaithersburg, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.